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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,512	11/16/2001	Oskar Axelsson	NIDN-10389	4557

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,512	AXELSSON ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/20/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,48,52-57,61,64 and 67* is/are pending in the application.

4a) Of the above claim(s) *45 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-57,61,64 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 11/15/2006, in reply to the Office Action mailed 6/15/2006, is acknowledged and has been entered. The Response, filed 9/20/2007, in reply to the Requirement for Election/Restriction mailed 8/20/2007, is also acknowledged and has been entered.

Election/Restrictions

Applicant's election without traverse of Group II in the reply filed on 9/20/2007 is acknowledged. Claims 45, 48, 52 - 57, 61, 64 and 67 are pending, of which claims 45 and 48 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 52 - 57, 61, 64 and 67 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments, see page 8 of the Response filed 11/15/2006, with respect to the Double Patenting rejections over claims 35, 40, 41, 46, 47 and 66 have been fully considered. The rejections have been WITHDRAWN in view of the cancellation of claims 35, 40, 41, 46, 47 and 66.

Applicant's arguments, see page 8 of the Response filed 11/15/2006, with respect to the objection to claims 39 and 49 have been fully considered. The objections have been WITHDRAWN in view of the cancellation of claims 39 and 49.

Applicant's arguments, see page 9 of the Response filed 11/15/2006, with respect to the rejection of claims 45 and 52 under 35 USC 112, first paragraph, have been fully considered. The rejections have been WITHDRAWN in view of the amendment filed 11/15/2006.

Applicant's arguments, see page 9 of the Response filed 11/15/2006, with respect to the rejection of claims 47 and 52 under 35 USC 112, second paragraph, have been fully considered. The rejections have been WITHDRAWN in view of the cancellation of claim 47.

Applicant's arguments, see page 10 of the Response filed 11/15/2006, with respect to the rejection of claims 35, 36, 38 – 40 and 42 - 43, have been fully considered. The rejections have been WITHDRAWN in view of the cancellation of claims 35, 36, 38 – 40 and 42 - 43.

Applicant's arguments, see page 10 – 11 of the Response filed 11/15/2006, with respect to the rejection of claims 41, 44, 45, 47, 49 - 60, 62, 63 and 65, have been fully

considered. The rejections have been WITHDRAWN in view of the amendment filed 11/15/2006.

Allowable Subject Matter

The indicated allowability of claims 61 and 64 is withdrawn in view of newly discovered reference(s). Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 61, 64 and 67 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Ardenkjaer-Larsen *et al.* (WO 98/58272).

Ardenkjaer-Larsen discloses polarised MR imaging agents containing proton or other non-zero nuclear spin nuclei, i.e. ^{13}C, ^{19}F, etc. (page 6, third paragraph). Such imaging agents are soluble in aqueous media. Conveniently, the MR imaging agent

once polarised will remain so for a period sufficiently long to allow the imaging procedure to be carried out in a comfortable time span (page 8). For in vivo use, a polarised solid MR imaging agent may be dissolved in administrable media (eg water or saline), administered to a subject and conventional MR imaging performed (page 10). Particular mention is made of 1,3,5-tricarboxybenzene as an MR imaging agent (page 12, second paragraph). Such a compound meets the instant claim limitations of containing a spin polarised I = ½ nucleus, having a molecular weight below 1000D and containing a cyclic chromophore. While Arden-Larsen does not specifically recite that the nmr spectrum for said I = ½ nucleus has a linewidth of less than 1 Hz, it is interpreted, absent evidence to the contrary, that said compound would inherently meet the claimed functional limitation of having the claimed NMR linewidth, because all of the structural limitations are met. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Claims 61, 64 and 67 are rejected under 35 U.S.C. 102(e) as being anticipated by Ardenkjaer-Larsen *et al.* (US 6,278,893).

Ardenkjaer-Larsen discloses methods of magnetic resonance investigation of a sample, preferably of a human or non-human animal body, said method comprising the

step of ex vivo polarisation of a high T_1 agent (abstract). Ex vivo methods of magnetic resonance imaging may be improved by using polarised MR imaging agents comprising nuclei capable of emitting magnetic resonance signals in a uniform magnetic field (eg MR imaging nuclei such as ^{13}C or ^{19}F nuclei) and capable of exhibiting a long T_1 relaxation time (column 1, lines 60+). Conveniently, the high T_1 agent once polarised will remain so for a period sufficiently long to allow the imaging procedure to be carried out in a comfortable time span (column 3, lines 49+). For in vivo use, a polarised solid high T_1 agent may be dissolved in administrable media (eg water or saline), administered to a subject and conventional MR imaging performed. Thus solid high T_1 agents are preferably rapidly soluble (eg. water soluble) to assist in formulating administrable media (column 4, lines 64+ - column 5). Preferred high T_1 agents are ^{13}C labeled and include those shown in column 6 – 12, several of which meet the instant claim limitations of being water soluble and containing a spin polarized I = ½ nucleus (i.e. ^{13}C), a cyclic chromophore and having a molecular weight below 1000D (see for example, ascorbic acid, uric acid, etc. While Arden-Larsen does not specifically recite that the nmr spectrum for said I = ½ nucleus has a linewidth of less than 1 Hz, it is interpreted, absent evidence to the contrary, that the high T_1 agents would inherently meet the claimed functional limitation of having the claimed NMR linewidth, because all of the structural limitations are met. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims

are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Claims 56 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Jeffries *et al.* (US 3,546,575).

Jeffries discloses a means for producing sizable nuclear polarizations in normal density matter at both room and low temperatures. By irradiating a crystal with circularly polarized light in combination with preferential relaxation and microwave resonance, enhancement is obtained of the polarizations of nuclei in hyperfine interaction with paramagnetic ions as well as of abundant nuclei at diamagnetic sites throughout the crystal (abstract). The invention involves placing the sample, either a crystal or liquid, in a magnetic field and irradiating it with circularly polarized light, as in optical pumping. In some instances, simultaneous irradiation with radio frequencies or microwave fields is also required. The angular momentum of the circularly polarized light is transferred to paramagnetic species in the sample. The invention gives the possibility of producing sizable nuclear polarization in solids at room temperatures. The apparatus does not require high power microwave oscillators or the use of highly uniform magnetic fields. Thus, the invention offers advantages in economy, efficiency and simplicity over the prior art. It is an object of the invention to provide a means for producing sizable nuclear polarization in solids for nuclear scattering experiments. It is another object of the invention to enhance the nuclear magnetic resonance signal so as to provide a greater signal-to-noise ratio for nuclear

magnetic resonance spectroscopy in applications to both solids and liquids (column 2, line 64+ – column 3, line 25). Figure 2 is an energy level diagram for a paramagnetic ion in a high field showing the populations obtained by the invention. In Figures 2 and 3 are shown energy level diagrams revealing the nuclear dynamics pertaining to the invention. Figure 2 portrays the levels and transitions for a paramagnetic ion in high field with an electron spin S= ½ and nuclear spin I = ½. The frequency required to induce transitions between levels 1 and 3 is defined as ν_{13}. The populations shown in column (a) are obtained by irradiating the crystal with circularly polarized light only and those in column (b) result from the additional presence of the RF field at frequency ν_{13} in the apparatus of Figure 1 (see column 4, lines 57+ and column 5 -7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 52 – 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ardenkjaer-Larsen *et al.* (WO 98/58272) in view of van Kesteran *et al.* (*Phys. Rev. Lett.*, 1985, 55, p. 1642 – 1644).

Ardenkjaer-Larsen discloses methods of magnetic resonance investigation of a sample, preferably of a human or non-human animal body using an MR imaging agent polarized via dynamic nuclear polarization using an OMRI contrast agent (see pages 4 – 5). The polarised MR imaging agents containing proton or other non-zero nuclear spin nuclei, i.e. ^{13}C, ^{19}F, etc. (page 6, third paragraph). Solid MR imaging agents (e.g. ^{13}C or ^{19}F enriched solids) may exhibit very long T_1 relaxation times and for this reason are especially preferred. The T_1 relaxation time may be several hours in the bulk phase, although this may be reduced by reduction of grain size and/or addition of paramagnetic impurities. The long relaxation time of solids advantageously allows the procedure to be conveniently carried out with less haste and is particularly advantageous in allowing the polarized solid MR imaging agent to be stored or transported prior to pharmaceutical formulation and administration. In one embodiment, the polarised MR imaging agent may be stored at low temperature *e.g.* in frozen form prior to administration (page 10). Such imaging agents are soluble in aqueous media. Conveniently, the MR imaging agent once polarised will remain so for a period sufficiently long to allow the imaging procedure to be carried out in a comfortable time span (page 8). For in vivo use, a

polarised solid MR imaging agent may be dissolved in administrable media (eg water or saline), administered to a subject and conventional MR imaging performed (page 10).

Accordingly, Ardenkjaer-Larsen teaches a method for the preparation of a spin polarized MR imaging agent comprising polarization of a solid MR imaging agent having a ^{13}C nucleus by means of an OMRI contrast agent, rather than by means of irradiation with light to generate a spin polarized MR imaging agent.

Van Kesteran discloses that dynamic nuclear polarization is a technique used to obtain highly polarized nuclear spins for polarized targets in high-energy physics and for the enhancement of NMR sensitivity in a variety of fields. Conventionally, samples are doped with a small amount of centers which are paramagnetic in the ground state, cooled to liquid helium temperature and placed in a strong magnetic field. Then electron spin polarization is transferred to nuclear spins by means of microwave irradiation. Unfortunately, paramagnetic centers perturb subsequent experiments on the polarized-nuclear spin system. Recently, it was shown that DNP can also be achieved by use of molecules that are diamagnetic in the ground state and paramagnetic in the photoexcited triplet state. This technique is called microwave-induced optical nuclear polarization (MIONP). A molecular crystal is doped with a small concentration of guest molecules, then UV light is applied which excites guest molecules from the diamagnetic ground state S_0 via the excited singlet state S_1 to the paramagnetic triplet state T_0. DNP takes place by the solid effect takes place by the transference of the triplet-spin polarization to the nuclear spins by means of a microwave field. The attraction of this technique is that perturbing paramagnetic

centers can be removed once the proton spins are polarized by shutting off the excitation light so that guest molecules decay from the triplet state to the diamagnetic ground state (page 1642).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize an alternative method of spin polarization of the solid MR imaging agents in the methods disclosed by Ardenkjaer-Larsen, such as by means of microwave-induced optical polarization, rather than DNP using an OMRI contrast agent. One would have been motivated to do so because van Kesteran teaches that such methods are useful when the presence of paramagnetic centers is undesirable (i.e. paramagnetic OMRI contrast agents must be separated from MR imaging agents before administration, as in the methods of Ardenkjaer-Larsen page 4). One would have had a reasonable expectation of success in doing so because van Kesteran teaches that such methods result in polarization which is comparable to that with systems with paramagnetic centers in the ground state (page 1644).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER